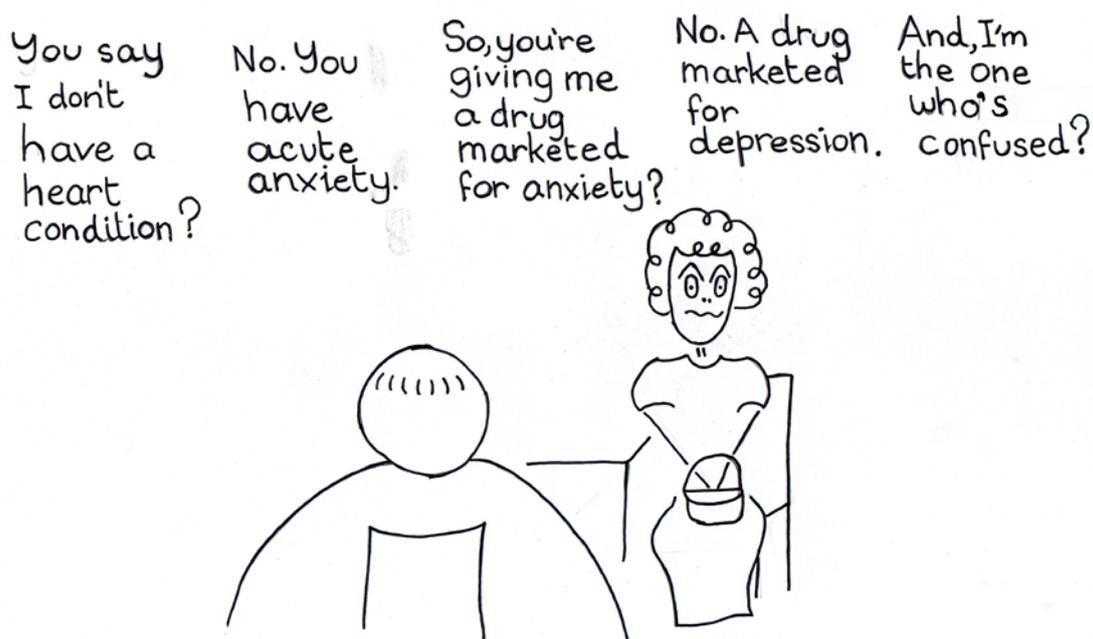


CHAPTER 17

ANTI-ANXIETY AND HYPNOTIC DRUGS



Introduction

Anxiety (or its equivalents: fear, arousal, worry) is ubiquitous. Anxiety (or its equivalents) has evolutionary value, alerting and motivating action (escaping) in dangerous situations.

Fear (anxiety) secondary to a stressor usually subsides with removal of the stressor. Pathological anxiety (fear when no stressor can be identified) fluctuates greatly in severity.

All individuals experience anxiety (or its equivalents) when faced with sufficient danger/stress.

Difficult questions arise: is it appropriate to “treat” normal reactions? If it is appropriate to treat “excessive” responses, how is excessive to be defined? In the view of the current author, in the current era, the doctors’ role is not simply to treat illness, but to provide medical help as requested (in keeping with professional standards).

For much of human history, anxiety has been (self) “treated” with alcohol and opium. These are addictive substances, and are best avoided.

The barbiturates came into clinical practice in 1903. They worked well for anxiety – however, they were highly addictive. They were also potentially fatal in overdose (respiratory depression) and were discontinued as a treatment of anxiety.

Other treatment for anxiety (bromides, meprobamate and chloral hydrate) were released but all were found to have unacceptable side effects and were discontinued.

The first of the benzodiazepine (antianxiety/hypnotic) family became available in 1960 (many others followed) and have been used to the present day.

The benzodiazepines have a rapid onset and are highly effective. However, there is a debate over whether they should continue to be recommended.

BENZODIAZEPINES

The benzodiazepines potentiate the actions of the widespread inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). The natural ligand/s for the benzodiazepine receptor is/are yet to fully identified (Baraldi et al, 2009).

The GABA A receptor is the gate keeper of a chloride channel. The benzodiazepine receptor is on the same protein molecule as the GABA A receptor. When a benzodiazepine occupies a benzodiazepine receptor, there is allosteric modulation of the GABA A receptor, such that the arrival of a molecule of GABA triggers the passage of a greatly increased quantity of chloride through the channel. Thus, the benzodiazepines are effective inhibitors because they make the endogenous inhibitor (GABA) more effective.

The benzodiazepines are safe in overdose and clearly superior to their predecessors in this regard. They are rapidly acting (relief may commence in 30 minutes) and effective in the treatment of anxiety (Rickels et al, 1993).

Tolerance develops – but to a questionable degree. There is no doubt that an individual begins to take benzodiazepines there may be some drowsiness, but this drowsiness disappears – this indicates that tolerance has developed to the hypnotic effect of the medication.

The claim is frequently made that tolerance also develops to the anxiolytic effects of the benzodiazepine. There is no evidence to support this claim. On the contrary, there is evidence that the anxiety reducing effects of the benzodiazepines is retained (Michelini, et al, 1996; Worthington et al, 1998).

Addiction may develop in those who abuse benzodiazepines for recreational purposes, or purposefully exceed treatment directions.

A benzodiazepine withdrawal syndrome has been described following cessation of standard therapy, featuring anxiety, dizziness and anorexia (Marriott & Tyrer, 1993). However, the difficulty is to distinguish such symptoms from the re-emergence of the original disorder. [It is noted that withdrawal symptoms are associated also with the SSRIs.]

Non-prescribed excessive use is associated with a severe withdrawal, which may feature vomiting, muscle twitching and convulsions.

The great benzodiazepine debate

[The current author is a supporter of the use of benzodiazepines in the treatment of anxiety disorders, and the following may not be without bias.]

Public health investigations claim that long-term benzodiazepine use is cause withdrawal symptoms and abuse, and in the elderly, falls, fractures (Bolton et al, 2008) and motor vehicle accidents.

Recent authoritative reviews/guidelines have focused on these public health issues and been moved to recommend that benzodiazepines use be ceased (Brandelow et al, 2008; Davidson, et al, 2010; Sivertsen et al, 2010; Davis et al, 2014; Gould et al, 2014; Bandelow et al, 2014; Mohatt et al, 2014; Janhsen et al, 2015; Olfson et al, 2015).

Instead, they recommend that cognitive behaviour therapy (CBT) should be the treatment of first choice, followed by the SSRIs, and the serotonin and noradrenalin reuptake inhibitors (SNRIs) and other non-benzodiazepine medications.

However, doctors have not ceased using benzodiazepines. For example, in British Columbia, in 2006, 8.4% of the population used a benzodiazepine (Cunningham et al, 2010). In Taiwan, recently, 20% of the population take an anxiolytic-hypnotic daily (Wang et al, 2013). The use of benzodiazepines in the USA remained unchanged from 2001 to 2007 (Rickels, 2013). The evidence suggests that benzodiazepines continue to be prescribed more frequently than the SSRIs in the treatment of anxiety (Sorsdahl et al, 2013).

How can this divergence between expert opinion/consensus statements/authoritative guidelines and clinical practice be explained? Most doctors find the benzodiazepines to be effective in the treatment of anxiety and insomnia and are 'sceptical' about the public health arguments that use should be discouraged (Cook et al, 2007). And, few believe that long-term benzodiazepine use poses a serious clinical threat (Olfson et al, 2015).

Barney et al (2009) states that "the major change of prescribing pattern from the benzodiazepines to newer antidepressants in anxiety disorders has occurred in the absence of comparative data of high level of proof". Cloos and Ferreira (2009) state that "benzodiazepines are still considered by many clinicians to remain good treatment options, in both the acute and chronic phase of the treatment of anxiety disorders, partially because of their rapid onset of action and their efficacy with a favourable side effect profile". Prominent expert, Karl Rickels (2013) states 'There is no evidence of superiority of newer antidepressants over the benzodiazepines in either long or short term treatment of anxiety. Benzodiazepine toxicity, adverse events and withdrawal symptoms, not better efficacy are cited in support of antidepressants over benzodiazepines; but the antidepressants are no better tolerated and also produce withdrawal symptoms.'

While there may be side effects such as falls in the elderly, this is only identified in huge studies and constitutes a 'public health concern', the benzodiazepines and highly effective and useful in clinical management of individual patients.

The benzodiazepines have been politicised. A social change occurred in the 1970s & 80s, and authority figures were no longer trusted as they had been formally. [Believe it or not, there was once a saying, "Doctor knows best". Sadly, this has long since lost currency.]

It was said that doctors did not listen to their patients, especially their female patients, and instead, prescribed them "Valium" as a disrespectful, easy solution. The benzodiazepines became stigmatized and have not recovered.



Illustration. Valium Spray, for general household uses: fighting, baby sitting, quietness, peace. This drawing was given to the author as a gift by a young female patient in 1998. The author believes the patient's conscious motives were positive. The reader may speculate about her unconscious motives.

Side-effects

Common

- Drowsiness (desirable in some circumstances)

Uncommon

- Dizziness (<1%)
- Ataxia (<2%)
- Respiratory depression (dose related)
- Disinhibition (may manifest as irritability)
- Cognitive deficits which impair work function (infrequent).

Toxicity

There is no evidence of toxicity in the adult. Overdose results in unconsciousness and rarely respiratory embarrassment. Problems may arise from other drugs concomitantly ingested. Benzodiazepine overdose may be reversed by iv flumazenil, remembering this agent has a very short half-life (7-15 minutes).

Use in pregnancy is not advised, although there is little evidence of teratogenesis. Use in the third trimester can precipitate a withdrawal syndrome in the newborn. Benzodiazepines are secreted in the breast milk and can cause drowsiness in the newborn.

Psychiatric uses

- Relief from anxiety disorders
- Relief from anxiety triggered by specific life events
- Relief from acute psychomotor agitation associated with psychosis and depressive disorders
- Relief from akathisia (unpleasant movement disorder secondary to antipsychotic drugs)
- Control symptoms of alcohol withdrawal

Preliminary work-up

There are no absolute contraindications to the use of benzodiazepines. In the case of current or past drug use disorder, the benzodiazepines are better avoided, in favour of drugs with lower abuse potential (SSRI, bupropion).

Determine the reproductive status of women.

Dose and monitoring

In view of the potential for misuse and the possibility of therapeutic tolerance, some authorities recommend the benzodiazepines be made available episodically, a few weeks at the most. While this is good advice, others advise that these drugs remain therapeutically active and can be safely used in the long-term (Pollack et al, 1993). Use the smallest dose which provides adequate relief.

Benzodiazepines must be used with caution in the elderly and the physically sick (especially those with liver disease and respiratory difficulties).

It is better to avoid driving and operating machinery until the impact of side-effects on the individual can be assessed.

Example drugs

There is a large range of benzodiazepines, with different potencies and half-lives.

The advantages of the long-acting drugs include less frequent dosing, less variation in plasma concentration, and less severe withdrawal. The disadvantages of the long-acting drugs include drug accumulation, and increased risk of daytime psychomotor impairment and drowsiness.

The advantages of the short-acting drugs include no drug accumulation and less daytime sedation. The disadvantages of the short-acting drugs include more frequent dosing and earlier and more severe withdrawal syndromes. Rebound insomnia and anterograde amnesia are thought to be a greater problem with the short-acting drugs.

Diazepam is a long acting drug; usual daily dose 5-40 mg. Can be given once daily, but is given in divided doses when using large doses.

Clonazepam is a long acting drug; usual daily dose 1.5-10 mg. Can be given once daily, or in divided doses.

Oxazepam is an intermediate acting drug; usual daily dose 30-60 mg. Usually given in divided doses, three times daily.

Temazepam is an intermediate acting drug which is exclusively marketed as an hypnotic. The usual nocte dose is 10 mg, but 20 mg is also used.

Alprazolam, which is structurally distinct from all other benzodiazepines, is given a separate paragraph because it has a relatively high potential for abuse. In many jurisdictions it is listed along with the highly restricted drugs (narcotics). An inhaled form is being developed which will have quicker onset but may increase addiction potential (Reissig et al, 2014).

BUSPIRONE

Buspirone is a 5HT-1A partial agonist. It suppresses activity in presynaptic serotonergic neurons, leading to diminished serotonin activity and down-regulation of some serotonin receptors. It has no muscle relaxant properties, no psychomotor or cognitive impairment, and is less sedating than the benzodiazepines. It does not potentiate the effects of alcohol (as can the benzodiazepines) and there is no withdrawal. The side-effects include headache, dizziness and nausea.

In formal clinical trials, buspirone is as effective as diazepam (Fulton & Brogden, 1997). The main clinical disadvantage is that the anxiolytic effect does not appear immediately, and may be delayed for at least 2 weeks. The benzodiazepines, on the other hand have an immediate effect. A second disadvantage is that buspirone is much

less effective when the patient has had prior exposure to a benzodiazepine. In clinical practice, and certainly when a rapid response is required, buspirone is rarely used in the treatment of anxiety (Hodge et al, 2012).

BETA-ADRENERGIC ANTAGONISTS

Where the symptoms are predominantly somatic and mediated by the sympathetic nervous system (palpitations, tremor and gastrointestinal overactivity), beta-blockade has been suggested. However, there is no evidence of efficacy and plenty of evidence of troublesome side effects; hypotension, bradycardia, excessive dreaming, bronchospasm, skin reactions and gastrointestinal upset.

Most authorities no longer recommend the use of beta-blockers in the treatment of anxiety.

A specific situation deserves mention. In states of high arousal, when an individual who needs steady hands (for example, a concert pianist about to go on stage) a single dose of a beta-blocker (propranolol, 40 mg) may have the desired effect. This is not a pathological state.

SEROTONIN REUPTAKE INHIBITION (SSRI & SNRI)

These drugs have been described in Chapter 16: Antidepressant drugs.

Most now regard these agents as first-line therapies for anxiety disorders (Lecrubier et al, 1997; Davis et al, 2014, Mohatt et al, 2014; Bandelow, 2014). Their effect is independent of the presence of depression. The effective dose in anxiety treatment is frequently higher than used in the treatment of depression. The antidepressants have the advantage of not being of interest to drug traffickers.

A recent meta-analysis of generalized anxiety treatments (Baldwin et al, 2011) found that **fluoxetine** was superior to various other drugs (including a benzodiazepine) in both response and remission; and that **sertraline** was the best tolerated.

The disadvantage relative to the benzodiazepines in the management of anxiety is that the onset of beneficial effect may take some weeks. In addition, there may be an initial, temporary worsening of anxiety. It has been stated that the SSRIs are associated with increased suicidality; this has not been properly substantiated and may be a confound of the occasional, initial worsening of anxiety symptoms, just mentioned.

Venlafaxine (SNRI) is effective in the treatment of anxiety (Davis et al, 2014; Bandelow et al, 2014). It is not without side-effects and withdrawal symptoms, but like the SSRIs, is of no interest to drug traffickers.

PREGABALIN

Pregabalin is structurally related to GABA. It is believed to inhibit calcium channel activity, leading to reduced neurotransmitter release, which in turn leads to reduced postsynaptic neuron excitability. Studies (Lydiard et al, 2009) have indicated anxiolytic effects comparable to the benzodiazepines. It appears to be effective in the treatment of social anxiety disorder and is recommended when other agents are ineffective or bring troublesome side-effects (Kawalec et al, 2014).

There is much interest in pregabalin because small abuse potential and it represents a new approach. It was recently approved as a treatment of anxiety in Europe (Bandelow 2013).

It is currently marketed around the world as a treatment of neuropathic pain and fibromyalgia. At the moment it is very expensive.

PSYCHOTHERAPY

Psychotherapy, of which cognitive behaviour therapy (CBT) is a current leading example, is effective in the treatment of anxiety (Allgulander et al, 2003).

Claims have been made that CBT is superior to pharmacotherapy in the treatment of anxiety disorders (Bandelow et al, 2014). Evidence is stronger for CBT than other forms of psychotherapy.

Claims have been made that CBT has a long lasting effect, persisting well beyond the treatment period. However, literature reviews have found no such evidence (Brandelow, et al, 2008).

It has been stated that the combination of CBT and pharmacotherapy provides a better outcome than either treatment alone. But this has not been supported by one literature reviews (Davidson et al, 2010) or a recent Cochrane Review (at least with respect to panic disorder; Watanabe et al, 2009).

However, general practitioners lack confidence in the use of in the use of psychological therapies such at CBT in the treatment of insomnia (Everitt et al, 2014).

HYPNOTICS

Benzodiazepines

Temazepam and **nitrazepam** continue to be marketed as hypnotics

Benzodiazepine-like hypnotic

Zolpidem is a non-benzodiazepine hypnotic which potentiates GABA by binding to the benzodiazepine receptor. Most frequently used hypnotic in the USA. It is effective in sleep initiation, but less effective in sleep maintenance.

There may be some risk of dependence, but probably less than with the benzodiazepines. Transient memory problems and, in depressed individuals, worsening of suicidal thinking, has been reported.

A study at the Mayo Clinic showed zolpidem significantly increases the risk of falls, and it is being discontinued at that hospital (Voelker, 2012). A recent review (MacFarlane et al, 2014) found that 'zolpidem is associated with rebound insomnia, complex sleep-related behaviours, and next-day residual effects (after middle-of-night dosing) on driving ability, memory and psychomotor performance'.

Initially, marketed as an immediate release agent, for short-term treatment (7-10 days) of insomnia. A controlled release form (CR) is now available, which is not restricted to short-term treatment. Dosage, immediate release 5-10 mg, CR 6.25-12.5 mg, shortly before bed.

ANTIPSYCHOTICS

Antipsychotic medications (quetiapine etc) have been used in the treatment of anxiety disorders (Hershenberg et al, 2014). However, due to potential serious side effects, this practice is strongly discouraged.

THE FUTURE

The search continues for an anxiolytic with the effects, but not the side-effects of the benzodiazepines (Skolnick, 2013).

A recent report (Herring et al, 2012) indicates a new direction. Orexin is a neurotransmitter which regulates arousal; and lack of it has been identified in cataplexy. Suvorexant is an orexin receptor antagonist, which appears useful in the treatment of primary insomnia.

Much anxiolytic research has focused on the GABAergic system – the chief brain inhibitory system. However, there is now some attention on the glutamatergic system – the chief brain activating system (Wieronska & Pilc, 2013).

Etifoxine is described as an anxiolytic and anticonvulsant drug, structurally distinct from the benzodiazepines. Although it has performed well in a comparison study with benzodiazepines (Stein, 2015) it has potentially serious side effects and may never be marketed for anxiety.

References

Allgulander C, Bandelow B, Hollander E, et al. WCA recommendations for the long-term treatment of generalized anxiety disorder. *CNS Spectrums* 2003; 8:53-61.

- Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalized anxiety disorder: systematic review and meta-analysis. *British Medical Journal* 2011; 342: d1199.
- Bandelow B, Boemer J, Kasper S et al. The diagnosis and treatment of generalized anxiety disorder. *Dtsch Arztebl Int* 2013; 110: 300-309.
- Bandelow B, Zohar J, Hollander E, et al. World Federation of Societies of Biological Psychiatry guidelines for the pharmacological treatment of anxiety, obsessive – compulsive and post-traumatic stress disorders – first revision. *The World Journal of Biological Psychiatry* 2008; 9:248-312.
- Bandelow B, Lichte T, Rudolf S, Witink J, Beutel M. The diagnosis of and treatment recommendations for anxiety disorders. *Deutsches Arzteblatt International* 2014; 111: 473-480.
- Baraldi M, Avallone R, Corsi L et al. Natural endogenous ligands for benzodiazepine receptors in hepatic encephalopathy. *Metabolic brain Disease* 2009; 24:81-93.
- Bolton J, Metge C, Lix L, Prior H, Sareen J, Leslie W. Fracture risk from psychotropic medications : a population-based analysis. *Journal of Clinical Psychopharmacology* 2008; 28: 384-391.
- Canadian Psychiatric Association. Clinical practice guidelines. Management of anxiety disorders. *Canadian Journal of Psychiatry* 2006; 51 (8 Suppl 2):9S-91S.
- Cloos J-M, Ferreira V. Current use of benzodiazepines in anxiety disorders. *Current Opinion in Psychiatry* 2009; 22:90-95.
- Cook J, Marshall R, Masci C, Coyne J. Physicians' perspectives on prescribing benzodiazepines for old adults: a qualitative study. *J Gen Intern Med* 2007; 22: 303-307.
- Cunningham C, Hanley G, Morgan S. Patterns in the use of benzodiazepines in British Columbia: examining the impact of increasing research and guideline cautions against long-term use. *Health Policy* 2010; 97: 122-129.
- Davidson J, Zhang W, Connor K, et al. A psychopharmacological treatment algorithm for generalized anxiety disorder (GAD). *Journal of Psychopharmacology* 2010; 24: 3-26.
- Davis M, Smits J, Hofmann S. Update on the efficacy of pharmacotherapy for social anxiety disorder: a meta-analysis. *Expert Opin Pharmacother* 2014; 15: 2281-2291.
- Everitt H, McDermott L, Leydon G, Yules H, Baldwin D, Little P. GPs management strategies for patients with insomnia: a survey and qualitative interview study 2014; 64:e112-9.
- Frampton J. Pregabalin: a review of its use in adults with generalized anxiety disorder. *CNS Drugs* 2014; 28: 835-854.
- Fulton B, Brogden R. Buspirone. An updated review of clinical pharmacology and clinical applications. *CNS Drugs* 1997; 7:68-88.
- Gould R, Coulson M, Patel N, Highton-Williamson E, Howard R. Interventions for reducing benzodiazepine use in old people: meta-analysis of randomised controlled trials. *Br J Psychiatry* 2014; 204: 98-107.
- Herring W, Snyder E, Budd K, et al. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology* 2012; 79:2266-2274.
- Hershenberg R, Gros D, Brawman-Mintzer O. role of atypical antipsychotics in the treatment of generalized anxiety disorder. *CNS Drugs* 2014; 28: 519-533.
- Hodge E, Ivkovic A, Fricchione G. Generalized anxiety disorder: diagnosis and treatment. *BMJ* 2012;345:e7500.
- Janhsen K, Roser P, Hoffmann K. The problems of long-term treatment with benzodiazepines and related substances. *Dtsch Arztebl Int* 2015; 112: 1-7.

- Kawalec P, Ciemiak A, Pilc A, Nowak G. Pregabalin for the treatment of social anxiety disorder. *Expert Opin Investig Drugs* 2014; 31: 1-10.
- Lecrubier Y, Bakker A, Dunbar G, Judge R. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. *Acta Psychiatrica Scandinavica* 1997; 95:145-152.
- Lydiard R, Rickels K, Herman B, Feltner D. Comparative efficacy of pregabalin and benzodiazepines in treating the psychia and somatic symptoms of generalized anxiety disorder. *International Journal of Neuropsychopharmacology* 2010; 13: 229-241.
- MacFarlane J, Morin C, Montplissir J. Hypnotics in insomnia: the experience of zolpidem. *Clin Ther* 2014; 36:1676-1701.
- Michellini S, Cassano G, Frare F, Perugi G. Long-term use of benzodiazepines: tolerance, dependence and clinical problems in anxiety and mood disorders. *Pharmacopsychiatry* 1996; 29:127-134.
- Mohatt J, Bennett S, Walkup J. Treatment of separation, generalized, and social anxiety disorders in youths. *Am J Psychiatry* 2014; 17: 741-748.
- Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry* 2015; 72: 137-42.
- Otto M, Smits J, Reese H. Cognitive-behaviour therapy for the treatment of anxiety disorders. *Journal of Clinical Psychiatry* 2004; 65(suppl 5):34-41.
- Pollack M, Otto M, Tesar G, et al. Long-term outcome after acute treatment with alprazolam or clonazepam for panic disorder. *Journal of Clinical Psychopharmacology* 1993; 13:257-263.
- Ressig C, Harrison J, Carter L, Griffiths R. Inhaled vs. oral alprazolam. *Psychopharmacology (Berl)* 2014 Sept 9 [Epub ahead of print]
- Rickels K, Downing R, Schweizer E, et al. Antidepressants for the treatment of generalized anxiety disorder: a placebo controlled comparison of imipramine, trazodone, and diazepam. *Archives of General Psychiatry* 1993; 50:884-895.
- Rickels K. Should benzodiazepines be replaced by antidepressants in the treatment of anxiety disorders? Fact or fiction? *Psychotherapy and Psychosomatic* 2013; 82: 351-352.
- Sivertsen B, Nordhus I, Bjorvatn S, Pallesen S. Sleep problems in general practice: a national survey of assessment and treatment routines of general practitioners in Norway. *J Sleep Res* 2010; 19: 36-41.
- Skolnick P. Anxiolytic: on a quest for the Holy Grail. *Trends Pharmacol Sci* 2012; 33: 611-260.
- Sorsdahl K, Blanco C, Rae d et al. Treatment of anxiety disorders by psychiatrists from the American Psychiatric Practice Research Network. *Rev Bras Psiquiatr* 2013; 35: 136-141.
- Stein D. Etifoxine versus alprazolam for the treatment of adjustment disorder with anxiety: a randomized controlled trial. *Adv Ther* 2015; 32: 57-68.
- Voelker R. Zolpidem increases patients fall risk, study shows. *JAMA* 2012; 308:2447.
- Wang L, Chen Y, Chen C et al. Trends in anxiolytic-hypnotic use and polypharmacy in Taiwan, 2002-2009. *Psychiatr Serv* 2013 Nov 15. doi: 10.1176/appi.ps.201300066.
- Watanabe N, Churchill R, Furukawa T. Combined psychotherapy plus benzodiazepines for panic disorder. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD005335. DOI: 10.1002/14651858.CD005335.pub2.
- Wieronska J, Pilc A. Glutamate-based anxiolytic ligands in clinical trials. *Expert Opin Investig Drugs* 2013; 22:1007-1022.

Worthington J, Pollack M, Otto M, et al. Long-term experience with clonazepam in patients with a primary diagnosis of panic disorder. *Psychopharmacology Bulletin* 1998; 34:199-205).